

### **REMARKS**

The Office Action dated July 18, 2008 has been received and carefully noted. The above amendments and following remarks are being submitted as a full and complete response thereto.

Claims 4, 5, and 7 have been rejected and claim 4 has been amended to correct its caption. Claims 1-3 and 6 have been cancelled. Thus, claims 4, 5 and 7 are pending in this application. Applicants respectfully request reconsideration and withdrawal of the outstanding objection and rejection.

#### **Objection**

Claim 4 is objected to because of informalities. In particular, the Office Action stated that the claim was amended in the Response filed on April 28, 2008 but the caption is still labeled as "original." Claim 4 is amended to be labeled "previously amended." Accordingly, Applicants respectfully request withdrawal of the objection to claim 4.

#### **Rejection Under 35 U.S.C. §103**

Claims 4, 5, and 7 are rejected under 35 U.S.C. §103(a) as being obvious over Del Soldato et al. (WO 95/30641, hereinafter "Del Soldato") in view of Ara et al. ("Cyclooxygenase and lipxygenase inhibitors in cancer therapy," *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 1996, 54, 3-16 hereinafter "Ara"). Applicants respectfully traverse this rejection.

The Office Action maintains that: (1) the results in the Declaration were expected

in view of the cited references; (2) there is no side-by-side comparison of the closest prior art; and (3) the Declaration is not commensurate with the scope of the claims, as the claims do not include the specific dosages of the Declaration (Office Action, page 5).

The Applicants submit that the results in the Declaration do indeed support the patentability of the invention and compare the closest prior art. As admitted in the Office Action, primary reference Del Soldato does not disclose or suggest the use of the claimed compounds for the treatment of gastrointestinal tumors. Rather, Del Soldato discloses the use of the compounds “as anti-inflammatory, analgesic, and anti-thrombotic activities,” and for use “in septic shock.” See pages 38-39 of Del Soldato. Del Soldato also discloses that the compounds are “inhibitors of cyclo-oxygenase (COX).” See page 1 of Del Soldato.

Secondary reference Ara discloses that “[t]he inhibition of cyclooxygenase and lipoxygenase activities by non-steroidal anti-inflammatory drugs and their effects on tumor growth and promotion have also been reported.” See page 3 of Ara. The specific non-steroidal anti-inflammatory drug “aspirin” is disclosed as “inhibit[ing] colon tumorigenesis in rodents.” See page 8 of Ara.

The Declaration compares Ara with the presently claimed invention by comparing the activity of aspirin and NO-derivatives of aspirin (specifically NO-Asp 1/2/3) on colon cancer cells. See Experiments 1 and 2-A of the Declaration. Thus, the Applicants disagree with the Office Action’s statement that the Declaration does not compare the closest prior art.

The Declaration shows that the NO-derivatives of aspirin perform better than aspirin in the colon cancer models. In these experiments, a lower number indicates

better results. In Experiment 1, the application of 18 mg/kg of NO-Asp-1 resulted in only 15% cancerous cell formation, while the application of 10 mg/kg of aspirin resulted in 40% cancerous cell formation. In Experiment 2-A, the application of 20  $\mu$ M NO-Asp-3 resulted in 50% cell proliferation; the application of 300  $\mu$ M NO-Asp-1 resulted in 40% cell proliferation; and the application of 10  $\mu$ M NO-Asp-2 resulted in 0% cell proliferation. On the other hand, the application of 500  $\mu$ M aspirin resulted in 100% cell proliferation, which was the same performance as the control (in other words, the aspirin had no effect at the tested concentration). Thus, the results presented in the Declaration clearly show the superior performance of the NO-derivatives of aspirin, as compared to aspirin. In particular, the Applicants submit that the NO-derivatives of aspirin are much more effective than the reference aspirin, even at very low concentrations. For at least these reasons, the Applicants submit that the Declaration evidence supports the patentability of the invention.

The Applicants do not believe that the Declaration evidence requires them to claim specific dosages of the compounds. The Declaration evidence was in the nature of concentration studies, where certain concentrations of the NO-derivatives were compared with certain concentrations of aspirin. These studies show that the invention works better than the prior art, but they do not support a requirement of a certain dosage level for effectiveness.

For at least the above reasons, Applicants respectfully submit that claims 4, 5 and 7 are not obvious over the proposed combination of Del Soldato and ARA. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 4, 5 and 7 under 35 U.S.C. §103(a) over Del Soldato in view of Ara.

**CONCLUSION**

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event that this paper is not being timely filed, the Applicants respectfully petition for an appropriate extension of time. Any fees for such an extension, together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account Number 01-2300, referencing Docket Number 026220-00039.

Respectfully submitted,



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